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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/665,111	SCHENDEL ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 23-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 23-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 have been canceled. Claims 23-42 have been added and are examined on the merits.

It is noted that the original claim set present on filing was drawn to the use of semi-allogeneic antigen presenting cells in contrast to the instant claims which are drawn to the use of haploidentical antigen presenting cells. The specification states on page 7 that HLA-haploidentical antigen presenting cells have one allele for each of HLA-A, B, C, DR, DQ and DP in common with the patient, wherein the alleles are on the same chromosome. The art recognizes that semi-allogeneic in context of antigen-presentation encompasses cells expressing at least one class I or class II MHC determinant that is allogeneic to the recipient and at least one class I or Class II MHC that is allogeneic to the recipient. Thus, the instant amendment claims have been narrowed in scope because it requires that at least one allele for al of HLA-A, B, C, DR, DQ and DP, rather than only one allele for HLA, B, C, DR, DP or DQ.

Claim Objections

Claim 41 objected to because of the following informalities: there is no space between "HLA" and "haploidentical", and there is a period before "and/or". Appropriate correction is required.

Claim 23 comprises an extraneous verb: "introducing proteins and/or peptides....are introduced".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28, 34, 39, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Claims 28 and 34 recite "preferably" ovarian, "preferably" cells of leukemias and lymphomas, "preferably" sarcomas, "preferably" melanomas and "preferably" blastomas. Claim 39 recites "preferably" selected from oncogenes, "preferably" HER2/neu, "preferably" PSMA, "preferably" WT-1, "preferably" MUC-1 and "preferably" telomerase. It is unclear whether these preferred species are required by the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 32 requires the composition of claim 32 which is a vaccine. .

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The art teaches that a vaccine must be prophylactic (Stedman's Medical dictionary, 2000, lines 1-3). The specification does not provide any teachings of the prophylaxis of cancer, how to determine the individuals who will develop a particular cancer, nor how to effectively prevent said particular cancer type before occurrence. Thus, one of skill in the art would not be able to use the composition of the invention as a vaccine without undertaking to determine how to select for individuals which will develop a particular cancer type before the said cancer occurs in the individual. The abstract of Wheeler (Salud p'ublica de M'exico, (1997 Jul-Aug) 39 (4) 283-7) teaches that a cancer vaccine against human papillomavirus for the treatment of cervical cancer

requires not only the activation of antigens and overcoming the host response, but the generation of high levels of T and B memory cells; and the persistence of antigens. The instant specification has not provided any teachings regarding the persistence of the tumor antigens in an individual who has yet to develop a specific type of cancer. Further Efferson et al (Anticancer research, 2005, Vol. 25, pp. 715-24) teach that efficient induction of memory cells is hindered by the lack of information about the relationship between TCR stimulation and the cytokines required for Ag-specific memory CD8+ cells and proliferation and survival. It is noted that the instant specification has not provided any evidence that adequate levels of T and B memory cells would persist in an immunized individual who has not developed a cancer, and Efferson et al is clearly discussing a need in the art as of 2005, therefore the enablement for how to generate adequate memory T and B cells can not be provided from the general knowledge of in the art. Bachman et al (Journal of Immunology, 2005, Vol. 175, pp. 4677-4685) teach that memory T cells are not a homogeneous population and can be divided into central memory T cells with a substantial capacity for recall proliferation and effector memory T cells with limited recall proliferation capacity. Bachman et al teach that the protective capacity of the different subpopulations of memory T cells vary, and the generation of the subpopulations is influenced by the nature and route of immune challenge. These references serve to demonstrate that the prior art is not mature with respect to how to elicit an effective prophylactic memory cell response that will persist in an individual not harboring a tumor cells and which would function to protect said individual from tumor cell development. Because the specification does not address the issues in the post-filing date art regarding how to elicit an effective memory cell response from the administration of the claimed compositions, and no objective evidence or working examples have been provided, one of skill in the art would be subject to undue experimentation in order to make and use the claimed composition as a vaccine.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 27, 28, 30, 31, 40 rejected under 35 U.S.C. 102(b) as being anticipated by Greenman et al (WO 99/03976).

Claim 23 is drawn in part to a method for the generation of HLA-haploidentical a\APC for the treatment of tumor diseases in a patient comprising providing antigen-presenting cells from a donor which are HLA-haploidentical with respect to that of the patient; introducing peptides which are over expressed in tumor cells or derived from autologous tumor cells into said HLA- haploidentical antigen-presenting cells. Claim 40 embodies the method of claim 23 wherein said antigen presenting cells are dendritic cells or macrophages

Claim 27 is drawn to the antigen-presenting cells obtained by a method according to claim 23. Claim 28 embodies the antigen presenting cells of claim 27 selected from carcinomas and hematopoietic cell tumors. Claim 30 embodies the cells of claim27 which are dendritic cells or macrophages. Claim 31 is drawn to a pharmaceutical composition containing HLA-haploidentical antigen-presenting cells. of claim 27.

Greenman et al disclose a method of treating a population of isolated leukocytes from a donor so as to render a portion of the population non-proliferating to the extent that the population causes minimal GVHD while still retaining sufficient immune function effective to promote destruction of a diseased cell or pathogen (abstract). Greenman et al disclose that a donor is identical genotypically in 3 or more of the 6 HLA loci of HLA-A, B, and DR, or, "haploidentical" Greenman et al disclose that a preferred embodiment is having a donor and host identical for HLA-A, B and DRB 1 (page 26, lines 26-27), which fulfills the limitation of claims 23 and 33 for haploidentical . Greenman et al disclose that antigen-presenting cells, which include dendritic cells (page 15, line 10), from donors can be pulsed with antigen characteristic of a diseased cell, or can be co-cultured with diseased cells(e.g., inactivated tumor cells); and these APCs can then be exposed to donor leukocytes prior to infusion of the donor leukocytes into a recipient (page 48, lines 1-4), which fulfills the requirement of introducing proteins or peptide which are over expressed in tumor cells into the donor antigen presenting cells . Greenman et al disclose that the invention is useful for the treatment of chronic

myelogenous, acute myelogenous, acute lympholytic, multiple myeloma and other forms of leukemia and myeloma, and the treatment of certain solid tumors, including breast lung, ovarian and testicular, prostate, colon, melanoma, renal carcinoma, neuroblastoma and head and neck tumors (page 19, lines 17-26), thus fulfilling the specific embodiments of claim 28

Claims 23, 27, 28, 30, 31, 33, 34, 37-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Cohen (WO98/33527, reference of the IDS filed April 29, 2004).

Cohen et al disclose a method of treating a tumor in a mammal comprising the administration of an immunogen comprising semi-allogeneic immunogenic cells (abstract and page 10, lines 1-5) Cohen et al disclose that the immunogenic cells of the invention encompass an antigen-presenting cell, such as a dendritic cell , which may be transformed with DNA encoding at least one antigen recognized by T-cells of the recipient (page 17, lines 1-6, page 18, lines 7-10 and page 18, lines 16-21). Cohen et al disclose that a preferred embodiment of donor specificities is unmatched in the range of about 50% to less than 100% (page 23, first full paragraph). In the instant specification on page 7 "haplospecific" is defined as having one allele for each of HLA-A, B, C, DR, DQ and DP in common with the patient. Thus the definition of the specification of having at least one allele in common, would be included in the preferred embodiment of Cohen requiring 50% unmatched alleles. Further Cohen et al disclose that in the case of a donor cell expressing only syngeneic determinant, said antigen presenting cell can be transformed to express an allogeneic determinant (page 17, lines 17-27) which fulfills the requirement of the specification regarding "haploidentical").

Cohen et al disclose that the introduction of DNA into antigen-presenting cells can be accomplished through various well known procedures such as by transfection of viral and retroviral vectors comprising the DNA, transduction into a cell of modified virus particles, and physical/chemical techniques such as calcium phosphate transfection, complex formation with polycations or lipids, electroporation, particle bombardment and microinjection into nuclei (page 29, first paragraph) and the incorporation of DNA or RNA encoding for at least one tumor antigen introduced into an antigen presenting cell (page 30, lines 1-3 and 7-8) as well as the transduction of tumor genomic DNA obtained from a tumor cell line or a tumor taken from a recipient into the antigen presenting cell (page 8, lines 8-11 and page 30, lines 11-16) which

fulfills the specific embodiment of introduction of DNA encoding proteins or peptide which are over expressed in tumor cells or are derived from autologous tumor cells into the haploidentical antigen presenting cells

Claims 27-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Kugler et al (Nature Medicine, 2000, Vol. 6, pp. 332-336, reference of the IDS submitted April 29, 2004).

Claims 27-31 are product by process claims. Section 2113 of the MPEP states

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.".

Kugler et al disclose a cell hybrid comprising a renal cell tumor and a dendritic cell from an allogeneic donor. The fused cell fulfills the specific embodiments of an antigen-presenting cell containing peptides from the renal cell carcinoma partner. Because the donor dendritic cells were fused with autologous tumor cells, it is reasonable to conclude that said cells would contain peptides present in at least two different tumor cell lines. When given the broadest reasonable interpretation, the cells of claims 27-31 carry no restrictions as to the identity of the recipient patient. The allogeneic dendritic cells disclosed by Kugler et al thus fulfill the embodiments of claim 23 because said cells would inherently have the property of being haploidentical with an unspecified patient.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23, 26-28, 30, 31, 33-35, 37-40 rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen (WO98/33527) in view of Kugler et al (Nature Medicine, 2000, Vol. 6, pp. 332-336).

Claims 26 and 35 embody the method of claim 23 and the method of claim 33, respectively, wherein antigen presenting cells of two different haploidentical individuals are used.

Cohen et al teach the limitations of claims 23, 27, 28, 30, 31, 33, 34, 37-40 for the reasons set forth above.. Cohen et al do not specifically teach two different haploidentical individuals for donor haploidentical antigen-presenting cells.

Kugler et al teach that different HLA-mismatched donors were recruited for each immunization to enable cognate tumor associated antigen-recognition by avoiding dominant allospecific responses (page 333, first column, lines 18-21).

It would have been prima facie obvious at the time the claimed invention was made to use two individual donor's haploidentical antigen presenting cells. One of skill in the art would have bee motivated to do so by the teachings of Kugler et al on desirability of avoidance of an allospecific response. One of skill in the art would understand that in the method of Cohen et al requiring at least on allogeneic determinant, an allospecific response would develop in a patient

that was unrelated to the anti-tumor response, and that if a different antigen presenting haploidentical cell were used for the second immunization having a different allogeneic determinant, this would result in avoidance of elaboration of the first allospecific response.

Claims 23, 25-28, 30, 31, 33-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen (WO98/33527) and Kugler et al (Nature Medicine, 2000, Vol. 6, pp. 332-336) as applied to claims 23, 26-28, 31, 33-35, 37-40, above, and in further view of Eastman et al (WO 01/36680) and Schuller et al (WO 02/36790).

Claims 25 and 36 embody the method of claim 23 and the method of claim 35, respectively, wherein the first RNA from tumor cells cDNA, the cDNA is amplified by RCR and transcribed into RNA.

Cohen et al teach the introduction of DNA into antigen presenting cells by viral transfection of vector comprising DNA. The combination of Cohen et al and Kugler et al does not teach the reverse transcription of amplified cDNA into RNA.

Eastman et al teach a method for preparing cRNA comprising amplification of cDNA (claim 3). Schuller et al teach a method of infected dendritic cells with influenza virus vector wherein said vector incorporates RNA (claims 1, 11 and 12 and page 19, lines 28-30).

It would have been prima facie obvious to substitute the influenza viral vector of Schuller et al comprising RNA obtained by reverse transcribing cDNA as taught by Eastman et al in the method rendered obvious by the combination of Cohen et al and Kugler et al. One of skill in the art would have been motivated to dos o by the teachings of Schuller et al on the transfection of dendritic cells with the influenza virus vector which incorporates RNA and the teachings of Eastman et al on the method of making cRNA, which would provide the RNA for incorporation into said vector.

Claims 23-31, 33-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen (WO98/33527) and Kugler et al (Nature Medicine, 2000, Vol. 6, pp. 332-336) and Eastman et al (WO 01/36680) and Schuller et al (WO 02/36790) as applied to claims 23, 25-28, 30, 31, 33-40, above, and in further view of Warnier et al (WO 98/58956).

Claim 24 embodies the method of claim 23 wherein proteins, peptides, RNA, DNA or cDNA from several different tumor cell lines are introduced into the haploidentical antigen-resenting cells. Claim 29 embodies the cell of claim 27 wherein said cell comprises p proteins, peptides, RNA, DNA or cDNA from several different tumor cell lines. Claim 41 embodies the method of claim 23 wherein proteins, peptides, RNA, DNA or cDNA from several different tumor cell lines are introduced into the haploidentical antigen-resenting cells. Claim 42 embodies the method of claim 41 wherein pooled cRNA from two or three different tumor cell lines is introduced.

Cohen et al teach the incorporation of DNA or RNA encoding for at least one tumor antigen introduced into an antigen presenting cell (page 30, lines 1-3 and 7-8) as well as the transduction of tumor genomic DNA obtained from a tumor cell line or a tumor taken from a recipient into the antigen presenting cell (page 8, lines 8-11 and page 30, lines 11-16). The combination of Cohen et al, Kugler et al, Eastman et al and Schuller et al do not specifically teach using polynucleotides or polypeptides from several different tumor cell lines, although Cohen et al does teach using at least one tumor antigen which is suggestive of using multiple tumor antigens.

Warnier et al teach that tumors express a set of tumor antigens, of which only certain subsets may be expressed in the tumor of any given patient and the desirability of having antigen-presenting cells expressing "polytopes" comprising multiple epitopes on tumor antigens in order to reflect a boarder spectrum of tumor associated antigens (page 20, line 31 to page 21, line 7)

It would have been prima facie obvious at the time the clamed invention was made to use haploidentical antigen presenting cells comprising polynucleotides from more than one tumor cell line. One of skill in the art would have been motivated to do so by the teachings of Warnier et al on the restricted expression of antigen on patient tumors. One of skill in the art would have been motivated to include the antigens from several different tumor cell lines in order to insure that the antigen –resenting cell would provide antigens which were expressed on the actual patient tumor.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 23-42 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-20 of copending Application No. 10/665,421. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
6/25/2006

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